## REMARKS/ARGUMENTS

Reconsideration of this application, as presently amended, is respectfully requested.

Support for the amendment is found in the specification on page 3, line 9-13, in which the adjuvant in the vaccine composition of the invention comprises a metabolizable oil in conjunction with aluminum hydroxide. On page 6, lines 4-6, the metabolizable oil includes "SP oil," the agent utilized in the working examples of the application and the declaration of record. As taught in the application, SP oil designates a particular oil emulsion comprising a polyoxyethylene-polyoxypropylene block copolymer, squalane, polyoxyethylene sorbitan monooleate and a buffered salt solution. On page 7, lines 26-29 and elsewhere, the application teaches that the treatment of the cattle is accomplished through parenteral administration.

Turning to the Office action, it is submitted that the Office erred substantively as to factual findings of conclusion of obviousness. Further, the Office totally misinterpreted case law and therefore inappropriately applied the substantive law to the facts of this application. Since the three art rejections are not fairly based on a correct analysis of the prior art or substantive law, they cannot be sustained.

For the first art rejection on the merits, the Examiner maintains the rejection of Claims 22-24 under 35 U.S.C. § 103(a) as being unpatentable over Doyle *et al.* (U.S. Patent No. 5,965,128) in view of Clancy *et al.* (U.S. 2004/0057965 A1) and further in view of the Sigma Catalog as set forth in the previous Office action and on pages 4-8 of the present Office action. Applicants respectfully traverse this rejection due to the following specific and distinct points:

1. The express teachings in the art were ignored contrary to the guidelines of M.P.E.P. § 2141.02 (prior art must be considered in its entirety, including disclosures that teach away from the claims) and M.P.E.P. § 2146 (references cannot be combined where reference teaches away from their combination) that make it clear that negative teachings must be considered by the Examiner. Even more current guidelines effective October 10, 2007 stress that "combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art."

In this rejection, to make and to use an injectable formulation for reducing shedding of *E. coli* O157:H7 in cattle as the inventors have done require that a person reasonably skilled in



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the prior art must totally ignore the express teachings of the primary reference of Doyle *et al.* that teaches away from use of an injectable formulation of *E. coli*.

Doyle *et al.* teaches that feeding non-pathogenic probiotic bacteria to cattle reduces the carriage of the harmful *E. coli* O157:H7 bacteria as a consequence of the competition in the rumen of the animal. However, Doyle *et al.* do not imply that probiotic bacteria can act in any way, shape or form as an injectable vaccine to reduce shedding.

Indeed, Doyle *et al.* expressly teach: "Vaccines are not likely to be effective in reducing the amount of *E. coli* O157:H7 carried and shed by cattle" (col. 2, lines 2-3). Although Doyle *et al.* say that vaccination has been the traditional approach to protecting cattle from carriage of harmful bacteria, they explain that there is difficulty in vaccinating cattle against *E. coli* O157:H7 because the strain does not adhere to or attach to colon tissue and does not infect cattle. As a consequence, Doyle *et al.* use the non-pathogenic dominant probiotic bacteria to reduce localization of *E. coli* O157:H7 in the rumen since they believe that the rumen is the most important site for long-term carriage of *E. coli* O157:H7, and may serve as the source of bacteria found in the colon.

Using common sense based on Doyle *et al.*, there is absolutely no question that one of ordinary skill in the art would be deterred from vaccinating cattle and accomplishing what Applicants have done. Particularly in view of the negative teachings of Doyle *et al.*, the practitioner would be discouraged from finding an injectable formulation for reducing shedding of *E. coli* O157:H7 in cattle. The practitioner would have no reasonable expectation of success in reducing shedding of *E. coli* O157:H7 through the administration of Applicants' vaccine composition and the stimulation of a strong immune response. It is quite unexpected, therefore, that Applicants demonstrated a significant reduction of pathogen prevalence in the hide and fecal samples of vaccinated cattle (see, for example, the working Example 3 on page 13 of the application).

2. The present amendment provides a further difference in the claimed method over the cited art. Applicants note that the currently presented claims specify that the vaccine composition is injected parenterally in the animal. An "injectable" formulation is a term of art, well-known to the ordinary practitioner in the pharmaceutical and veterinary fields. While



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Doyle *et al.* disclose that the bacteria can be formulated as an inoculant paste to be directly "injected" into an animal's mouth, the experimental illustration of using a syringe for oral administration does not propose the instant parenteral injection in any stretch of the imagination. Besides, to administer a paste formulation by true injection – as that term is commonly used in practice – would kill the animal. Thus, the claimed invention is further distinguished from Doyle *et al.* based on the recitation of "administering by parenteral injection" in the amended Claim 22.

3. The Office inaccurately represents Clancy *et al.* as supporting the administration of whole inactivated bacteria together with an adjuvant for the treatment of an intestinal infection. When the reference is read as a whole, the teaching of Clancy *et al.* is not applicable to the present invention and cannot sustain the rejection.

Clancy *et al.* solely relate to a vaccine composition for the prophylactic or therapeutic treatment of mucosal infections in the respiratory tract. The mucosally administrable composition of Clancy *et al.* only describes antigens that are respiratory tract pathogens, *i.e.*, those that normally colonize the respiratory tract (specifically, NTHi, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae, Staphylococcus albus* and *Staphylococcus aureus*). Clancy *et al.* purely teach respiratory tract vaccines, showing, for example, the immunization of rats against non-typeable *H. influenzae* (NTHi) by an intra-lumenal (IL) injection (into the lumen of the small intestine). Clancy *et al.* do not describe, exemplify or suggest any antigens that colonize the intestinal tract, let alone *E. coli* O157:H7.

In the patented invention, Clancy *et al.* mandate that their antigen be derived from at least one microorganism "which is capable of causing infection at a mucosal surface" [par. 005]. Doyle *et al.* explicitly state that *E. coli* O157:H7 does not adhere to or attach to colon tissue; and it is well known to the ordinary practitioner that *E. coli* O157:H7 does not infect cattle. As such, the antigen of the present invention is expressly and positively excluded from the composition of Clancy *et al.* since Applicants' antigen is not a microorganism capable of causing infection at the mucosal surface of the animal undergoing inoculation.

There is absolutely no scientific reason to predict that the mucosally administrable composition of Clancy *et al.* could work with the whole cells of inactivated or killed *E. coli*



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O157:H7 to reduce shedding in the feces of cattle. Thus, the Examiner cannot justify a finding that the ordinary artisan could have recognized that the results of the claimed combination were predictable. To the contrary, one of ordinary skill in the art based on his/her knowledge of the art and common sense would appreciate that there is no way of knowing whether the injectable formulation of whole *E. coli* O157:H7 could reduce shedding of *E. coli* O157:H7 without substantial experimentation. The results are simply not predictable in view of the cited art.

4. The excerpt from the Sigma catalog in and of itself does not prove obviousness. It only shows that numerous adjuvants are known in the art. However, the person of ordinary skill in the art would have had no reason to select this particular page 1472 of the catalog without the claimed invention first in hand as a road map. A generic list of adjuvants from one chemical supplier's catalog does not provide any teaching of which particular adjuvant can be used in concert with which antigen for what results. The sheer infinite number of adjuvants that are commercially available from a multitude of sources makes selection of an adjuvant an enormous task. Without some direction as to exact combinations matching up adjuvants to active ingredients for a particular purpose, a long list of adjuvants does not describe or predict the excellent results of the Applicants' claimed composition or vaccine of an injectable *E. coli* O157:H7. The only reason one would be motivated to find a metabolizable oil on this specific page of the Sigma catalog would be through impermissible hindsight vision, having the claimed invention already at hand. The pure fact that the ordinary practitioner needs to pick and choose among a huge variety of options means that the reference does not render the present invention obvious.

5. The Examiner has misinterpreted case law by ignoring the complete picture and therefore inappropriately applied the substantive law to the facts of this application.

On page 4, the Examiner cites the KSR case for the premise that it allegedly forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obvious and mentions the recent Board decision in *Ex parte Smith*. This comment is copied as an excerpt from the prosecution history of U.S. Patent Application No. 11/436,775 and provided by the Office under examination guidelines. It is not established case law since the T-S-M approach is still a viable option if the circumstances warrant the rationale.



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It is interesting to point out that the Board is also citing KSR to rebut *prima facie* cases of obviousness and overturn rejections where "common sense" dictates that the claimed invention was not obvious.

It is further important to note that KSR did not change the Examiner's obligation to articulate an adequate rationale for combining the prior art to attain the claimed invention. How a person of ordinary skill in the art would have understood the prior art teachings continues to be a significant factor in the equation. In fact, the U.S. Supreme Court in the KSR case reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co.*

None of the cases cited by the Examiner in the Office action apply to the facts at hand. For example, *Ex parte Smith* dealt with an apparatus invention in which the Board held that it was obvious to glue two separate sheets to form a continuous two-ply seam as taught in the art, rather than folding one sheet to create a seam along the folded edge, as taught by another cited patent; and it would have been obvious to improve a pocket insert by creating two pockets from a single pocket using an additional line of adhesive. However, in that case, the claim limitation of "continuous two-ply seams" and the function it performed, to create a pocket, were identical between the claimed invention and the prior art. Thus, the selection of the continuous two-ply seam of one reference over the folded seam of another represented an obvious choice within the skill of the art, that is, a choice between known viable alternatives.

The *Ex parte Smith* case is being used by the Office for the principle that a simple substitution of one known element for another to obtain predictable results is obvious. To make that conclusion, the Examiner must find at the very least that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components and one of ordinary skill in the art could have substituted one known element for another, and the results of the simple substitution would have been predictable. These two basic findings are not applicable to the facts of the present application. In this case, the issues do not deal with a simple substitution of one known element for another. Rather, the ordinary practitioner must make several modifications of the cited prior art to arrive at the claimed invention. Consequently, the



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decision and case law from *Ex parte Smith* case are not controlling in the instant situation.

On page 5, the Examiner has also inappropriately cited the *Bristol-Meyers Squibb*, 01-CV-1867, slip op. in which the district court found the patent in litigation valid due to a purpose-based distinction. Subsequently, the U.S. Court of Appeals for the Federal Circuit (CAFC 06-1021) reversed that earlier district court decision due to anticipation reasons. The case involved claims to a mixture of an anesthetic sevoflurane and water to avoid a Lewis Acid degradation reaction in which an earlier patent disclosed the same mixture of sevoflurane and water. The CAFC confirmed the established principle that new uses for known processes may be patented, but a prior art device cannot be patented, even if new uses of it are found. Nevertheless, the *Bristol-Meyers Squibb* case relating to anticipation does not apply to the obviousness issues at hand.

In sum, taking the invention as a whole and examining the cited references in their entirety, it is clear that one of ordinary skill in the art would not arrive at the claimed invention from the teachings of the combined references. First and foremost, Doyle *et al.* and Clancy *et al.* do not teach methods for reducing the shedding of *E. coli* O157:H7 in an animal through active immunity, *i.e.*, inoculating cattle with an effective vaccine composition. Secondly, it cannot be inferred from either of these two references that a vaccine containing inactivated or killed whole cells of *E. coli* O157:H7 would work against *E. coli* O157:H7. Based on the negative teachings of Doyle *et al.* and the limited respiratory tract vaccine of Clancy *et al.*, the practitioner could not anticipate being able to achieve a superior immune response to the unique vaccine formulation comprising whole cells of *E. coli* O157:H7 in conjunction with the adjuvant comprising SP oil and aluminum hydroxide. The combined references simply fail to teach or suggest all claim limitations of Applicants' method.

For the second art rejection on the merits, the Examiner rejects Claims 22-24 under 35 U.S.C. § 103(a) as being unpatentable over Doyle *et al.* (U.S. Patent No. 5,965,128) in view of Clancy *et al.* (U.S. 2004/0057965 A1) and further in view of the Sigma Catalog as applied to Claims 22 and 23 and further in view of Molly *et al.* (U.S. 2005/0084500 A1) as set forth in the previous Office action and on pages 8-11 of the present Office action. Applicants respectfully traverse this rejection due to the following specific and distinct points:



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1. The arguments given herein above to refute the first rejection apply equally to refute the application of this second rejection. As the Examiner notes that the rejection is an obviousness rejection over the combination of references, if Doyle *et al.* in view of Clancy *et al.* and further in view of the Sigma Catalog fail to teach all of the claim limitations of the method of Claim 22, the collective art in further view of Molly *et al.* cannot reach to the level of the invention of dependent Claim 23.

2. The Office failed to determine the scope and factual content of Molly *et al.* and, in so doing, neglected to ascertain the true differences between the claimed invention and the prior art. Molly *et al.* relate solely to a growth promoter composition suitable for animals that comprises a fungus and at least one growth-promoting component comprising organic acids, inorganic acids, animal feed antibiotics, conventional growth promoters or plant extracts. The fungus is taught by Molly *et al.* as an essential feature of the art composition that is present in the composition in an amount from about 50% to about 99.9% by weight. The only working example in Molly *et al.* shows the influence of *Lentinus edodes* in combination with a growth-promoting component on the growth and feed conversion ratio (FCR) of chickens and pigs.

The Examiner points out that the instant claim recites open claim language and thus does not exclude other materials such as fungus from being present in the claimed composition. However, to add the fungus component in the art-taught amount of 50% to 99.9% w/w to the present invention would significantly alter the structure and intent of the claim recited method for reducing shedding of *E. coli* O157:H7. Since the fungus is taught by Molly *et al.* as a growth-promoting component, the selection and addition of fungus in an attempt to successfully achieve the reduction of shedding of *E. coli* would not make sense. Besides, the ordinary practitioner would not know what to expect from the co-administration of a substantial quantity of fungus with the neomycin medicated feed supplement in addition to the injectable formulation recited in Claim 22. The fact that the results would not be predictable to one of ordinary skill in the art, the combination of references in further view of Molly *et al.* would not render the claimed method obvious.

Additionally, the Examiner indicates that the reference teaches administering the animal feed antibiotic to improve intestinal function against enteric pathogens. Cattle do not need to



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improve intestinal function against enteric pathogens such as *E. coli* O157:H7 since they are not pathogenic to cattle, *i.e.*, clinical disease is not caused by *E. coli* O157:H7 in the animals shedding the bacteria.

In sum, the combined references do not teach or suggest all of the limitations of Claim 23. Neither Doyle *et al.* nor Clancy *et al.* teach an injectable vaccine containing whole cells of *E. coli* O157:H7. There is no suggestion or motivation in either reference to combine their teachings with the Sigma catalog and make a precise selection of the SP oil and aluminum hydroxide out of numerous commercially available adjuvants from Sigma and elsewhere. Certainly, Molly *et al.* do not add the motivation to select and use neomycin in combination with an injectable vaccine for reducing shedding of *E. coli* O157:H7. Particularly owing to the negative teachings of Doyle *et al.* and the lack of any basis to expect that the claimed injectable method would be successful in reducing the shedding of *E. coli* O157:H7, this rejection cannot be sustained.

For the third art rejection on the merits, the Examiner rejects Claim 22 under 35 U.S.C. § 103(a) as being unpatentable over Johnson *et al.* ("Effect of vaccination of dairy calves with an inactivated *E. coli* O157:H7 bacterin on shedding of E. coli O157:H7," Food and Environmental Safety Posters, 1999, Abstract 40aP) in view of the Sigma Catalog as set forth in the previous Office action and on pages 11-15 of the present Office action. Applicants respectfully traverse this rejection due to the following specific and distinct points:

1. The Office erred by not determining the scope and factual content of Johnson *et al.* and, as a consequence, failed to ascertain the real differences between the claimed invention and the prior art. By ignoring the true vaccine composition taught by Johnson *et al.*, the Examiner did not make a proper finding that the prior art included each element claimed. In other words, the teachings of Johnson *et al.* taken in view of the Sigma Catalog do not reasonably lead the ordinary artisan to the actual combination of the claimed elements.

The Examiner asserts that the instant claim recites open claim language and thus does not exclude other materials (*i.e.*, inactivated verotoxin 2 and intimin O157) from being present in the claimed composition. She assumes that merely because Johnson *et al.* mention a study involving shedding of *E. coli* O157:H7 that the reference meets the claim limitation of reducing



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shedding of *E. coli* O157:H7 in an animal by way of the present method. This analysis of the content of the cited art is inaccurate and leads the fact finder to the wrong conclusion.

In looking at what the cited art teaches in its entirety, one would see a totally different vaccine composition taught by Johnson *et al.* than recited in the instant claims. Since there is a scientific basis for the inclusion and requirement of the inactivated verotoxin 2 and intimin O157 in the vaccine of Johnson *et al.*, the ordinary practitioner would not omit the two important immunogenic factors from the formulation. Good judgment would make the practitioner conclude that such omission would have dire effects on the immunogenicity properties of the vaccine. After all, verotoxin 2 is a known Shiga toxin produced by *E. coli*. The protein is made up of two subunits: one is responsible for toxic action and the other, for binding to a specific cell type. Verotoxin requires highly specific receptors on the host cells' surface to attach and enter the cell. Cattle do not carry these receptors and, consequently, they shed the bacteria in their feces without being infected by the bacteria. Intimin O157, extracted from the outer membrane of *E. coli* O157:H7, is a bacterial protein that permits the *E. coli* to adhere to the host's intestinal cell walls. The bacteria require intimin to colonize their host, attach themselves to intestinal tissue and cause human disease. Much research has been placed on developing vaccines that prevent the transmission of the bacterial protein intimin to the host cell. It follows that Johnson *et al.* would formulate a study using a vaccine that employs intimin O157 along with the Shiga toxin in an attempt to produce antibodies against *E. coli* O157:H7 and the study would suggest to subsequent researchers to pursue a vaccine containing a combination of the extracted intimin O157 and Shiga toxin.

While Johnson *et al.* clearly do not propose the bare use the whole cells of *E. coli* O157:H7 in the absence of the other two critical active components, using common sense would lead the ordinary artisan to question the appeal of omitting verotoxin 2 and intimin O157 from the vaccine composition of Johnson *et al.* Particularly where verotoxin 2 and intimin O157 are art-recognized as vital for bacterial activity, one of ordinary skill in the art could not predict the immune effect of injecting the whole cells of *E. coli* O157:H7 without verotoxin 2 and intimin O157. There would be no way of knowing whether the whole cells of *E. coli* O157:H7 alone would even elicit an immune response until tested. As such, the reasonable



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expectation of success when injecting a vaccine composition containing only the whole cells of *E. coli* O157:H7 in the absence of verotoxin 2 and/or intimin O157 would be totally missing.

Regarding the amount of shedding allegedly obtained by Johnson *et al.* and the Examiner's assumption that the study was successful, it is interesting to find that others do not hold the same opinion. See the commentary in "The Prevalence of E. coli O157:H7 in Cattle" in the Food Safety Network relevant to the cited reference published as a poster abstract (http://www.foodsafetynetwork.ca/en/article-details.php?a=3&c=10&sc=74&id=270):

> A study funded by the Ontario Cattlemen's Association in 1998 evaluated the effect of vaccinating dairy calves against E. coli O157:H7 on shedding in the manure. In this study, led by Dr. Scott McEwen at the University of Guelph, the vaccinated calves did not shed significantly fewer bacteria than the control calves that were not vaccinated (Johnson et al. 1999 [Effect of Vaccination of Dairy Calves with an Inactivated E. coli O157:H7 bacterin on Shedding of E. coli O157:H7 (unpublished)]). Dr. McEwen feels more investigation needs to be done to determine if vaccination against E. coli O157:H7 can be effective. "Other methods of attacking this organism in the gut of cattle may be more effective," he said.

It is also pertinent to this rejection based on the primary reference of Johnson *et al.* to mention that the competition has been researching the effectiveness of a vaccine that contains a bacterial extract of *E. coli* O157:H7 type III secreted proteins. With knowledge of this commercial information and the failure of Johnson *et al.* to reduce shedding, the practitioner in the veterinary field having common sense at the time of the invention would not think to utilize whole cells of *E. coli* O157:H7 alone in an injectable vaccine formulation as the Applicants have done with success.

Contrary to the Examiner's belief that the rejection can be sustained because Applicants' composition may contain extra ingredients such as verotoxin 2 and intimin O157, the analysis of the cited art should properly focus on the critical point that the ordinary practitioner must omit the two active elements taught in the vaccine composition of Johnson *et al.* in order to modify the cited reference and arrive at the claimed invention. Ordinary logic makes one presume that Johnson *et al.* used the least number of elements in their vaccine composition in an attempt to achieve shedding results. By eliminating the two active elements of Johnson *et al.* from the claim-recited composition while obtaining effective shedding results, Applicants found a new and useful vaccine composition that is not suggested by the reference.



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2. The rejection cannot stand because neither Johnson *et al.* nor the Sigma Catalog describe or suggest the selection of the specific adjuvant administered in the claimed method for use with *E. coli* O157:H7 and the claim-recited combination produce unexpected results. The claim limitations, namely, the particular, unique combination of whole cells of *E. coli* O157:H7 in conjunction with the adjuvant comprising SP oil and aluminum hydroxide are totally missing from the collective art.

Certainly, it is appreciated that the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. However, the opposite premise applies in the case at hand. The claim-recited combination of known elements is not obvious because it yields unpredictable results.

It is clear from the working examples of the application that Applicants' innovative selection of adjuvant in their vaccine composition provides unexpected activity. Example 2 provides evidence that the metabolizable oil combination adjuvant in the vaccine of the present invention (Group 7) provided the greatest overall serological titers and the best improvements in immunity. Equally unexpected under the circumstances, the animals displayed minimal, normal reactions at the vaccine administration sites indicating that the injectable vaccine formulation was surprisingly safened in the presence of a strong immune response.

Working Example 3 on page 13 of the application further demonstrates that the vaccine reduced pathogen prevalence by 31.1% in fecal samples. The animal study published by the National Cattlemen's Beef Association, previously supplied to the Office, shows how the percent of positive *E. coli* O157:H7 isolates in the fecal sample of the control (45.8%) was substantially reduced in the vaccinated group (14.7%). The percent of positive *E. coli* O157:H7 isolates on the hide sample of the control (40.3%) was also considerably reduced in the vaccinated group (20.0%). One could not reasonably predict from Johnson *et al.* in view of the Sigma Catalog that the claim-recited vaccine composition would be able to stimulate a cell-mediated immune response and effectively reduce shedding to a significant degree in the absence of verotoxin 2 and intimin O157.

Furthermore, there is no suggestion advanced in the art to combine the teachings and suggestions of Johnson *et al.* with a specific catalog offering a multitude of known chemical



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ingredients, plus omit two active ingredients of Johnson *et al.*, to suggest the present invention except from using Applicants' invention as a template through hindsight reconstruction of Applicants' claims.

3. The rejection cannot be sustained in view of the inventor's declaration substantiating the experimental evidence set forth in the application and demonstrating that the formulation of the invention elicits a strong immune response yet surprisingly provides a minimal injection site reaction that avoids the anticipated adverse impact on meat quality. Considering the failure of the vaccine of Johnson *et al.* to reduce shedding in dairy cows, the objective evidence of unexpected results of the claimed composition clearly refutes any contention of *prima facie* obviousness.

To address the Examiner's concerns on page 14 of the Office action with respect to the showing, the claims have been amended for the better readability thereof and to ensure that the claimed subject matter is commensurate in scope to the evidence in the declaration.

The benefit of Applicants' vaccine formulation to infuse active immunity in the cattle against shedding and to obtain strong antibody titers that prevent colonization of the *E. coli* O157:H7 plus provide bactericidal effect is not suggested in the collective art.

Turning now to the new grounds of rejection, the Examiner has rejected Claim 24 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement for reasons given on pages 15-19 of the Office action. Without comment as to the merits of the rejection but to expedite matters, the present amendment defines the metabolizable oil adjuvant combination as SP oil and aluminum hydroxide in accordance with the working examples of the application. Since the amendment overcomes this rejection, it is respectfully asked that the Examiner withdraw the rejection pursuant to Section 112.

In view of the foregoing remarks and the present amendment, Applicants respectfully request that all of the rejections be withdrawn.

If any outstanding issue remains, the Examiner is invited to contact the undersigned attorney for a discussion of mutually agreeable solutions.



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Accordingly, Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

WYETH

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